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EXAMINER	
LEE, JAE W	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,786	DEPERTHES ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9,10,17,28-34,36,38-42,46-59 and 62-69* is/are pending in the application.

4a) Of the above claim(s) *41,51,53,55,57,59,62,66 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,9,10,17,28-34,36,38-40,42,46-50,52,54,56,58,63-65,68 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In response to the previous Office action, a restriction requirement (mailed on 01/30/2009), Applicants filed a response and amendment received on 07/27/2009. Said amendment canceled Claims 1-5, 7, 8, 11-16, 18-27, 35, 37, 43-45, 60 and 61, amended Claims 6, 9, 10, 17, 28, 32-34, 38-42, 46-59 and 62, and added Claims 63-69. Thus, Claims 6, 9, 10, 17, 28-34, 36, 38-42, 46-59 and 62-69 are at issue and present for examination.

Applicants' arguments filed on 12/12/2007 and 07/27/2009, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election

Applicant's election with traverse of Group I, alpha 1-antichymotrypsin (ACT), and SEQ ID NO: 14 with modified Reactive Serpin Loop sequence Val367 Lys368 Ile369 Thr370 Phe371 Arg372 Ser373 Ala374 Leu375 Val376 Glu377 Thr378 (VKITFRSALVET), is acknowledged.

The traversal is on the ground(s) that the shared technical feature is "a serpin sequence with a modified Reactive Serpin Loop (RSL) having amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces PI with an arginine (R) or a lysine (K) and creates a substituted PI-P' 1 scissile bond (emphasis added)" as particularly claimed in amended claim 39. Examiner has emphasized the fact that the Group 1 serpin sequences and the Group 2 amino acid sequences contain molecules that are "structurally distinct." It is the Applicant's position that both the Group 1 serpin sequences and the Group 2 amino acid sequences are well within the accepted scope of Markush practice, which represents a situation that is subject to special procedural rules under the MPEP. MPEP 1850.III.B states, in part, the following: When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled: (A) All alternatives have a common property or activity; and (B) (1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or (B) (2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains. In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common

structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together. In paragraph (B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved. The fact that the alternatives of a Markush grouping can be differently classified should not, taken alone, be considered to be justification for a finding of a lack of unity of invention. Applicant's contend that serpins, as members of a well characterized, discrete protein family containing recognized protein domains with recognized biological functions represent a valid Markush grouping by any of the accepted measures listed under MPEP 1850.III.B. They have a common activity as serine protease inhibitors and a common structural element embodied by the RSL, so they meet the A and B(1) criteria. Even if one were to argue that their common structure could not be a unifying criteria, they clearly belong to a recognized group of compounds by virtue of their classification as members of the serpin family, and therefore also fulfill the B(2) requirements. One of ordinary skill in the art would certainly expect that members of the group would behave in the same manner in the context of the invention. Similarly, Applicants contend that the Group 2 amino acid sequences are also within the accepted scope of Markush practice for the same reasons. Furthermore, Applicants allege that Chagas et al. does not disclose "a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein."

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Although Applicants allege that Group 1 serpin sequences and the Group 2 amino acid sequences are well within the accepted scope of Markush practice, the Examiner disagrees. Specifically, the invention as claimed fails to meet the criteria for Markush practice as set forth in MPEP 1850.III.B which states, in part, the following:

> When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled: (A) All alternatives have a common property or activity; and (B) (1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or (B) (2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains. In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together. In paragraph (B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention.

The Examiner notes that the invention as claimed fails to meet criteria as set forth in (B)(1) because **a common structure is NOT present in the modified RSL as claimed in claim 39** since its scope encompasses those RSLs with all of the amino acid residues within P6-P'6 substituted with any amino acid residues while P1 is either R or K (emphasis added). As such, a significant structural element is NOT shared by all of the alternatives. Furthermore, the invention as claimed fails to meet criteria as set

forth in (B)(2) because **there is NOT an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention** (emphasis added). In support of this notion, the Examiner points out the Table V of the specification on page 32, which discloses the inhibitory profile of these modified RSL, which is **different** with respect to various proteases as shown in the left column. For instance, ACT8.2 as set forth in SEQ ID NO: 16 and ACT5.18 as set forth in SEQ ID NO: 21 (see Table IV) inhibit hK2 95% and 73%, respectively, which **do not behave the same way** when compared to ACT6.2, ACT8.3 and ACT6.7 which inhibit hK2 at 100%. As such, one of skill in the art would NOT have expected that these various modified RSLs would behave the same way in the context of the claimed invention.

Taken together, the invention as claimed is not regarded as a proper Markush group for the reasons as explained above, and based on the fact that these modified RSLs are structurally distinct molecules, even if there is no prior art reference which anticipates the invention as claimed, there is no "special technical feature" shared between the groups as explained in the previous office action. For the reasons provided herein and in the previous office action, the restriction requirement is deemed proper.

Claims 41, 51, 53, 55, 57, 59, 62, 66 and 67 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claims 9 and 10 are objected to because of the following informalities:

The previous objection of Claims 9 and 10 are maintained for containing non-elected subject matter. It is noted by the Examiner that previously objected claim 41 is withdrawn from further consideration on the merits.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejections of Claims 10, 28 and 39-43 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn because Applicants have deleted the noted phrases.

Claims 17, 40, 42, 63-65, 68 and 69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17, 40, 42, 63-65, 68 and 69 are indefinite and unclear because claim 40 depends from claim 63 which depends from claim 40. In the interest of advancing prosecution, claim 17 is interpreted to depend from clam 39, and claims 63 and 68 to depend from claim 39.

Claims 50, 52, 54, 56 and 58 recite the limitation "the additional amino acid substitutions" in claim 39 and 47. There is insufficient antecedent basis for this limitation in the claim. In the interest of advancing prosecution, the noted claims are not given any patentable weight.

Claims 68 and 69 are unclear and indefinite in the recitation of "the amino acid substitutions are modified by at least one additional substrate active site sequence" and "the substituted pentapeptide sequences are modified by at least one additional substrate active site sequence". Since the "substrate active site sequence" is defined as "a sequence found on a substrate and which is a preferential recognition site for a protease" according to page 7 lines 7-8 of the specification, it is unclear how a recognition sequence, i.e., "substrate active site sequence", can modify amino acid substitutions or other peptide sequences. In the interest of advancing prosecution, the noted claims are not given any patentable weight.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 9, 10, 17, 28-34, 36, 38-40, 42, 46-50, 52, 54, 56, 58, 63-65, 68 and 69 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46. In response to this rejection, Applicants have canceled Claims 1-5, 7, 8, 11-16, 18-27, 35, 37, 43-45, 60 and 61, amended Claims 6, 9, 10, 17, 28, 32-34, 38-42, 46-59 and 62, and added Claims 63-69, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that recombinant inhibitor proteins encompassed by the genus of amended claims 39- 41 and 43 require both structural, i.e., a serpin and a modified RSL comprising a pentapeptide, and functional, L e., kallikrein inhibition, features in accordance with the written description requirement. The specification teaches the relationship between the structural features of the claimed proteins and their functions. For example, Table IV describes examples of RSLs which contain pentapeptides within the P6-P6' region of the RSL, each of which confer kallikrein inhibiting properties to the serpin in which said sequences are included (see inhibition results described in Tables V and VI and Example 1). Amended claims 39, 40, 41, and 43 are drawn to a genus of

kallikrein inhibiting recombinant inhibitor proteins having modified RSLs which comprise pentapeptides that confer improved inhibition of kallikrein top the protein. Applicant respectfully submits that there is sufficient written description in Applicant's specification regarding the claimed kallikrein inhibiting recombinant inhibitor proteins to inform a skilled artisan that Applicant was in possession of the claimed invention at the time the application was filed. Applicant also respectfully submits that a representative number of species within the claimed genus is disclosed in the specification to satisfy the written description requirement. As amended, claims 39, 40, 41, and 43 require that the recombinant inhibitor protein comprise a serpin and a pentapeptide, which the specification teaches confers kallikrein inhibiting properties to the serpin protein. The specification provides numerous examples of pentapeptides that may be used in the invention (see for Example Table 1). The specification also provides working examples which describe how to make six different recombinant inhibitor proteins comprising serpin proteins having modified RSLs, i.e., ACT comprising six variant pentapeptides (see pages 26 to 29). The specification also describes that the six ACT proteins having modified RSLs are more effective at inhibiting a kallikrein versus wild type ACT having an unmodified RSL (see Example 1, including Tables IV - VI). Not only does the specification provide working examples, but Applicant also teaches how to screen for additional pentapeptides that may be used in the recombinant inhibitor proteins of the invention, including phage display screening (see page 22, line 1 to page 23, line 14 and page 28). Applicant further teaches advantageous positions for the pentapeptides within the RSL (see, for example, Tables I and IV). Pages 23-24 and the working

examples of the specification teach how to introduce the pentapeptides into the serine protease, which is essentially used as a scaffold for the pentapeptide. With respect to the Examiner's suggestion that the working example describing ACT is not a representative number for the claimed genus, Applicants respectfully disagree. As described in MPEP 2163, The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. (emphasis added) The specification not only describes six versions of ACT having pentapeptides which inhibit kallikrein, but also provides teachings regarding additional serpins which may be used in the invention. For example, at pages 10-12 and Table II, the specification describes examples of serpins other than ACT known in the art which may be used in the recombinant inhibitor proteins of the invention. It is known in the art, as described at pages 2-3 of the specification, that serpins have similar structural features, including an RSL.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of the claims encompass a genus of recombinant inhibitor proteins, or inhibiting fragments thereof, which inhibits a

kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having *any amino acid substitutions* within the P6-P'6 interval, *wherein said serpin sequence can be attached to any amino acid sequence at N- and/or C-terminal ends,* which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P' 1 scissile bond (emphasis added). For considering whether or not representative species have been disclosed by the specification, the total number of variants of a modified RSL having any amino acid substitutions can be calculated from the formula $N!x19^{A}/(N-A)!/A!$, where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions for a specific % identity. Thus, for a variant of the modified RSL, the total number of variants to be tested is $12!x19^{11}/(12-11)!/11!$ (the modified RSL has 12 amino acids; 11 substitution positions) or $1.40x10^{15}$ variants without taking into consideration for the variability of P1 position.

Given [1] the unpredictability associated with predicting the structure of a polypeptide based on its function, or predicting the function of a polypeptide based on its structure (see Kisselev et al, 2002; Witkowski et al, 1999; and Wishart et al, 1995), and [2] the limited disclosure of the specification which is limited to a handful of modified RSLs (see Table IV on page 29 of the specification), one of skill in the art would have recognized that Applicants were in possession of over $1.40x10^{15}$ possible variants of RSL, having any amino acid sequence at N- and/or C-terminal ends, or any inhibiting fragments thereof which exhibit the desired biological function as recited in the claim, i.e., which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive

Serpin Loop (RSL) having any amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, and creates a substituted P1-P' 1 scissile bond.

Therefore, given the lack of additional representatives of the genus of recombinant inhibitor proteins, or inhibiting fragments thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having any amino acid substitutions within the P6-P'6 interval, wherein said serpin sequence can be attached to any amino acid sequence at N- and/or C-terminal ends, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P' 1 scissile bond as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 6, 9, 10, 17, 28-34, 36, 38-40, 42, 46-50, 52, 54, 56, 58, 63-65, 68 and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for a modified

recombinant inhibitor protein, α1-antichymotrypsin (ACT), comprising the amino acid sequence as set forth in SEQ ID NO: 14, does not reasonably provide enablement for any recombinant inhibitor proteins, or inhibiting fragments thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having any amino acid substitutions within the P6-P'6 interval, wherein said serpin sequence can be attached to any amino acid sequence at N- and/or C-terminal ends, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P' 1 scissile bond. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 6, 9, 10, 17, 28-34, 36, 38-43 and 46. In response to this rejection, Applicants have canceled Claims 1-5, 7, 8, 11-16, 18-27, 35, 37, 43-45, 60 and 61, amended Claims 6, 9, 10, 17, 28, 32-34, 38-42, 46-59 and 62, and added Claims 63-69, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 have been amended to require structural features identified by Applicant as imparting improved kallikrein specificity. It is known in the art, and the specification teaches, that serpin proteins have an active site called an RSL which is highly conserved in structure and plays a role in the binding of target proteinases (see page 2 line 25 to page 3, line 20). The specification also teaches the importance of the P1-PI' bond of the RSL, as the

specificity of serpins may be attributed to the residues at positions P 1-P 1' (see page 2, lines 25-32). Applicant provides working examples which describe kallikrein substrates identified using phage display, which may be used in the RSL of a serpin to improve specificity of the serpin for a kallikrein, e.g., hK2. The specification provides numerous examples of such pentapeptide sequences, including, for example, Tables I and IV. Tables I and IV both show that an arginine or a lysine at P1 of the RSL is important for increasing the binding affinity of the recombinant inhibitor protein for a kallikrein. The examples from Tables I and IV also describe the regions within the RSL which may be substituted by a pentapeptide specific for kallikrein, e.g., P5 to P'4, P3 to P2', and P4 to P'I. Applicant also provides a working example of six recombinant inhibitor proteins comprising different modified RSLs that have improved binding affinity for kallikrein. Thus, the specification provides numerous examples of modified RSLs which may be used to arrive at the claimed invention. In addition to the examples provided in the specification, Applicant also teaches how to identify other modified RSLs which may be used and how to make recombinant inhibitor proteins comprising a serpin and a modified RSL. As described above, the specification teaches at pages 22-23, that that peptides having improved specificity for kallikrein may be identified using a number of techniques, including combinatorial chemical libraries, immobilized peptide libraries, and phage display technology. Applicant also provides a working example of phage display technology in Example 1 at page 28, where six pentapeptides were identified and corresponded to changes in the RSL at positions P3-P3' (also described in Table IV). Applicant also teaches multiple other serpins which may be used in the proteins of the

invention, including, for example, the serpins described in Table II. Thus, the specification not only teaches the important features of the RSL which may be modified to improve binding affinity for a kallikrein, it also provides describes how to make recombinant inhibitor proteins which incorporate these feature.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of the claims encompass any recombinant inhibitor proteins, or inhibiting fragments thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having *any amino acid substitutions* within the P6-P'6 interval, *wherein said serpin sequence can be attached to any amino acid sequence at N- and/or C-terminal ends*, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P' 1 scissile bond (emphasis added). In order to illustrate how broad the scope of the claims are, the total number of variants of a modified RSL having any amino acid substitutions can be calculated from the formula $N!x19^{A}/(N-A)!/A!$, where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions for a specific % identity. Thus, for a variant of the modified RSL, the total number of variants to be tested is $12!x19^{11}/(12-11)!/11!$ (the modified RSL has 12 amino acids; 11 substitution positions) or $1.40x10^{15}$ variants without taking into consideration for the variability of P1 position.

Given [1] the unpredictability associated with predicting the structure of a polypeptide based on its function, or predicting the function of a polypeptide based on

its structure (see Kisselev et al, 2002; Witkowski et al, 1999; and Wishart et al, 1995), and [2] the limited guidance of the specification which is limited to six modified RSLs (see Table IV on page 29 of the specification), undue experimentation would be required for one of skill in the art screen over $1.40x10^{15}$ possible variants of RSL, having any amino acid sequence at N- and/or C-terminal ends, or any inhibiting fragments thereof in order to determine which ones, out of over $1.40x10^{15}$ possible variants of RSL, exhibit the desired biological function as recited in the claim, i.e., which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having any amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, and creates a substituted P1-P' 1 scissile bond.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any recombinant inhibitor proteins, or inhibiting fragments thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having any amino acid substitutions within the P6-P'6 interval,

wherein said serpin sequence can be attached to any amino acid sequence at N- and/or C-terminal ends, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P' 1 scissile bond, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 46, 47, 49, 50, 52, 54, 56, 58, 68 and 69 are rejected under 35 U.S.C. § 102(b) as being anticipated by Schechter et al. (Reaction of Human Chymase with Reactive Site Variants of alpha 1-Antichymotrypsin, Journal of Biological Chemistry, 1993, 268(31): 23626-23633) in view of an evidentiary reference, Rubin et al. (Cloning, Expression, Purification and Biological Activity of Recombinant Native and Variant Human alpha1-Antichymotrypsins, Journal of Biological Chemistry, 1990, 265(2): 1199-1207).

The rejection was stated in the previous office action as it applied to previous claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43 and 46. In response to this rejection, Applicants have canceled Claims 1-5, 7, 8, 11-16, 18-27, 35, 37, 43-45, 60 and 61, amended Claims 9, 17, 28, 32, 33, 38-40, 42 and 46, and added Claims 47-69, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Schechter reference cited by the Examiner does not teach each and every element of claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46, as required under 35 U.S.C. § 102(b). Schechter et al. describe single mutations within the ACT protein, as well as a hexamer substitution at P3-P3', to determine the impact of said mutations on ACT's ability to inhibit chymase. Applicant's invention is based on pentapeptides which are included in the RSL of recombinant inhibitor proteins and impart advantageous binding properties to the recombinant inhibitor protein such that the protein has improved binding affinity for kallikrein. There is no teaching or suggestion in Schechter et al. that the recombinant proteins described therein would have an increased affinity for kallikrein, as kallikrein is quite distinct from chymase described in the cited reference. The Schechter reference also does not teach recombinant inhibitor proteins comprising pentapeptides within the RSL, as required by independent claims 39, 40, and 43.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Contrary to Applicants' allegation that the claims are not anticipated because Schechter et al. do not teach recombinant inhibitor proteins comprising pentapeptides within the RSL, it is noted by the Examiner that such

limitation is NOT recited in the claims rejected herein. Instead, the claims are drawn to a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P'1 scissile bond. As such, the teachings of Schechter et al. and Rubin et al. meet the limitation of the claims because they teach a recombinant inhibitor protein ACT having a serpin sequence comprising a modified reactive serpin loop with a substitution at L358R (rACT-L358R), which is at P1 position, thereby creating a scissile bond, which is the amide bond linking the P1 and P'1 residues (see abstract of Rubin et al.). It is also noted that it is an inherent characteristics of the rACT-L358R to have increased binding affinity for the kallikrein.

The examiner has presented evidence to reasonably support the determination that the recombinant inhibitor protein of the prior art is encompassed by the claims. According to MPEP 2112.V, once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, specifically with respect to "increased binding affinity for the kallikrein", the burden is on the applicant to show a novel or

unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Conclusion

Claims 6, 9, 10, 17, 28-34, 36, 38-40, 42, 46-50, 52, 54, 56, 58, 63-65, 68 and 69 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656